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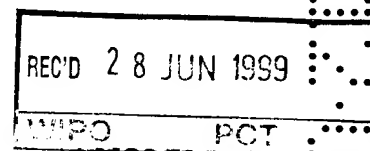
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Konstrukcija cevnega modula večjih volumnov

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KONSTRUKCIJA CIM CEVNIH MODULOV VEČJIH VOLUMNOV

Predmet izuma je konstrukcija CIM (Convective Interaction Media) cevnih modulov večjih volumnov uporabnih za preparativno ločitevanje in biokonverzijo.

Čiščenje in izolacija molekul, posebno biopolimerov, predstavlja še danes eno najdražjih stopenj v njihovem pridobivanju. Med biopolimere prištevamo oligopetide in polipeptide, proteine, encime, lektine, protitelesa, nukleinske kisline, polisaharide, oligonukleotide ter polinukleotide.

Obstaja več metod čiščenja kot so npr. izsoljevanje z nevtralnimi solmi, s spreminjanjem pH vrednosti, z elektroforezo in z uporabo kromatografskih metod.

Verjetno prva separacija proteinov je bila izvedena leta 1954 (A.J.P. Martin in R.L.M. Synge, Biochem. J., 35 (1941) 1358) na DEAE celulozi. Od tedaj je potekal intenziven razvoj tako kromatografskih nosilcev, kot tudi različnih kemijsko aktivnih skupin za ločevanje. Konec petdesetih let je predstavilo podjetje Pharmacia (Uppsala, Švedska) zamrežen dekstranski gel za t.i. gelsko filtracijo (angl. size-exclusion chromatography) za ločevanje proteinov in nukleinskih kislin (Nem. patent 1,292,883; GB patent 974,054). Njegovo uporabo v kromatografiji je omejevala predvsem nizka mehanska stabilnost. Leta 1976 je objavljena prva ločitev peptidov na osnovi t.i. kromatografije reverzne faze (K. Tsuji, J.H. Robinson, J. Chromatogr., 112 (1976) 663), čemur so sledili mnogi članki o ločevanju proteinov s pomočjo kromatografije, tako na osnovi gelske filtracije, ionsko-izmenjevalne kromatografije ter kromatografije na reverzni fazi. Uporabljeni nosilci so bili mehansko zelo stabilni in so omogočali visoke pretoke ter s tem krajšanje časa ločevanja. Imeli so zgradbo kroglastih delcev premera nekaj 10 do $100\mu m$ z visoko poroznostjo, kar je imelo za posledico veliko specifično površino ter s tem povezano visoko kapaciteto vezave biopolimerov.

Biopolimeri so velike molekule (tipično nekaj 10 do nekaj 100 kDa), zato je njihov difuzijski koeficient nizek (reda velikosti 10^{-7} m^2/s). Ker večina procesa ločevanja poteka v porah delčnih nosilcev, znotraj katerih tekočina miruje, potujejo molekule do aktivne površine na osnovi difuzije, ki hitrosti ločevanja omejuje. Zato so bili razviti nosilci različnih struktur, s katerimi naj bi odpravili težave povezane z difuzijo. Prvo tako rešitev predstavljajo neporozni delci (za pregled glej npr. W.-C. Lee, J. Chromatogr. B, 699 (1997) 29), kjer ves proces ločevanja poteka na površini neporoznega delca. To omogoča izredno hitre analize biopolimerov (nekaj sekund), vendar je njihova poglavitna slabost nizka specifična površina in zato nizka kapaciteta

vezave. Drugo rešitev predstavljajo t.i. pretočni delci (N.B. Afeyan, N.F. Gordon, I. Mazsaroff, L. Varady, S.P. Fulton, Y.B. Yang, F.E. Regnier, J. Chromatogr., 519 (1990) 1). Njihova značilnost je, da imajo poleg zaprtih por tudi pretočne pore. Za razliko od neporoznih delcev imajo višjo specifično površino ter kapaciteto vezave in boljše hidrodinamske lastnosti od poroznih delcev. Ker pa imajo delčno strukture, se med delci še vedno nahaja prazen prostor. Ker le-ta predstavlja nižji upor tekočini, jo večina (preko 90%) še vedno teče okoli delcev. Naslednji korak v razvoju nosilcev predstavljajo monoliti. Za razliko od prej omenjenih nosilcev, ki so v obliki delcev, so monoliti sestavljeni iz enega kosa poroznega polimernega materiala, ki vsebuje pretočne pore (US Patent, 4,889,632; US Patent 4,923,610). Ker znotraj nosilca ni praznega prostora, je celotna tekočina prisiljena teči skozi pretočne pore. Odlikujejo se po sposobnosti hitre separacije biopolimerov (primerljivi z neporoznimi delci), nizkim povratnim pritiskom tudi pri višjih pretokih ter visoki kapaciteti. Njihovo uporabo v industrijskih aplikacijah so dosedaj omejevale težave priprave monolita s homogeno strukturo večjih dimenzij, kot tudi slabša mehanska stabilnost. Rešitvi teh dveh problemov sta predmet tega patenta.

CIM cevni moduli so zgrajeni iz ohišja, podrobno opisanega v patentni prijavi št. P-9800058, ki zagotavlja mehansko stabilnost in dobro distribucijo ter monolitnega poroznega polimera v obliki cevi. Monolitni porozni polimer vsebuje majhne pore premera pod 200 nm kot tudi velike pore premera od 2500 nm. Poroznost monolitnega poroznega polimera je okoli 30 do 90%. Monolitni porozni polimer vključuje polimer polivinilnega monomera izbranega izmed divinilbenzena, divinilnaftalena, divinilpiridina, alkilen dimetakrilata, alkilen diakrilata, hidroksialkilen dimetakrilata, hidroksialkilen diakrilata, oligoetilen glikol dimetakrilata, oligoetilen glikol diakrilata, vinilestra polikarboksilne kisline, diviniletra, pentaerytritol di-, tri- ali tetrametakrilata ali akrilata, trimetiloilpropan trimetakrilata ali akrilata, alkilen bis akrilamida ali metakrilamida oziroma njihovih mešanic.

Monolitni porozni polimer vključuje tudi kopolimer polivinil monomera in monovinil monomera. Slednji je izbran iz skupine, ki vključuje stiren, stiren s substitucijo na obroču, vinilnaftalen, akrilate, metakrilate, vinilacetat, vinilpirolidon oziroma njihovo mešanico.

Poleg monomerov vsebuje začetna monomerna mešanica še radikalski iniciator, ki ga skupaj z monomeri raztopimo v inertnem organskem topilu iz skupine alkoholov, estrov karboksilnih kislin ali ketonov oziroma njihove kombinacije, s katerimi dosežemo različno poroznost končnega polimera.

Radikalski inicijator izberemo iz skupine azo spojin, peroksidov, hidroperoksidov, redoks sitemov ali podobno.

Na monolitni porozni polimer lahko s kemijsko modifikacijo vnesemo reaktivne kemijske skupine kot npr. alilne, amino, sulfonatne, hidrogensulfonatne, hidroksilne, ali alkilne dolžine do 18 atomov. Prav tako lahko nanje imobiliziramo različne ligande kot npr. peptide, proteine oligonukleotide, itd.

Delovni volumen CIM cevnega modula opisanega v patentni prijavi št. P-9800058 je premajhen za uporabo v večini industrijskih procesov. Volumen lahko v primeru CIM cevnega modula povečujemo na dva načina: z daljšanjem cevnega modula ali z večanjem njegovega premera. Kljub temu, da je s stališča kvalitete ločevanja bolj primerna prva možnost, pa se moramo zavedati, da volumen z daljšanjem narašča linearno, medtem ko z večanjem premera narašča kvadratno. Dodaten problem pri daljšanju CIM cevnega modula je enakomerna porazdelitev vzorca, saj je pot, ki jo mora vzorec prepotovati, da bi prekril celotno površino od začetka do konca cevnega modula, zelo dolga. Iz tega neizogibno sledi, da mora nadaljnje povečevanje, vsaj do neke mere, temeljiti na večanju premera.

Pri tem se pojavi problem zagotavljanja homogenosti strukture polimera. Polimerizacija je namreč eksotermen proces. Pri suspenzijski polimerizaciji ta pojav ni posebno problematičen, saj je prisotno mešanje, hkrati pa so kapljice, znotraj katerih polimerizacija poteka, majhne. Pri polimerizaciji večjih cevnih modulov pa pride do generiranja večje količine toplote, kar ima za posledico ustvarjanje temperaturnega profila znotraj polimerizacijske raztopine. Pri polimerizaciji monolitnega poroznega polimera iz katerega so CIM cevni moduli narejeni, lahko pride do gel-efekta, zato je generiranje toplote v kratkem času še toliko večje. Ker je struktura porazdelitve por od temperature močno odvisna, določa priprava polimera s homogeno strukturo zgornjo temperaturo znotraj polimerne zmesi, ki ne sme biti presežena med polimerizacijo.

Prav tako je za vzpostavitev nadzorovane strukture potrebno mirovanje monomerne mešanice. Iz tega sledi, da bo temperaturni profil znotraj polimera tekom polimerizacije odvisen od količine specifične generirane toplote, toplotne prevodnosti polimerne zmesi ter debeline polimernega sloja. Ker sta prva dva faktorja karakeristiki posameznega polimernega sistema, nanju ne moremo vplivati. Zatorej moramo določiti debelino sloja, znotraj katerega je sprememba temperature dovolj nizka, da ne vpliva na homogenost strukture polimera. Maksimalno temperaturo znotraj monolitnega poroznega polimera, ki ima obliko cevi termostatiranega na temperaturo polimerizacije

na notranji in zunanji strani, pri danem notranjem in zunanjem polmeru, izračunano na osnovi poznavanja toplotne prevodnosti polimerne mešanice in sproščene specifične toplote na osnovi enačbe:

$$T_{max} = T_0 + \frac{S}{4\lambda_T} \cdot \left[r_z^2 + \frac{r_z^2 - r_n^2}{2\ln\left(\frac{r_z}{r_n}\right)} \cdot \left(\ln\left(\frac{1 - \left(\frac{r_n}{r_z}\right)^2}{2\ln\left(\frac{r_z}{r_n}\right)} \right) - 1 \right) \right] \tag{1}$$

r_n - notranji premer (m)

r_z - zunanji premer (m)

T_0 - temperatura polimerizacije (K)

T_{max} - maksimalna dosežena temperatura znotraj polimera (K)

S - specifična sproščena toplota (W/m^3)

λ_T - toplotna prevodnost polimerne mešanice (W/mK)

V primerih, ko je premer dovolj velik, da je napaka sprejemljiva, lahko namesto enačbe 1 uporabimo enačbo za ravno ploščo, ki se glasi:

$$T_{max} = T_0 + \frac{S \cdot \left(\frac{r_z - r_n}{2}\right)^2}{2 \cdot \lambda_T} \cdot \left[1 - \frac{\left(\frac{r_n + r_z}{2}\right)^2}{\left(\frac{r_z - r_n}{2}\right)^2} \right] \tag{2}$$

Gornji dve enačbi ne vključujeta zunanjega toplotnega upora modela v katerem polimerizacija poteka, kot tudi ne toplotnega upora mejnega sloja medija v katerega je kalup z mešanico monomerov vstavljen. V primeru, ko so ti upori znatni, moramo gornje enačbe ustrezno modificirati.

Iz enačbe 1 oziroma 2 lahko za predpisano dovoljeno maksimalno temperaturo z numerično rešitvijo določimo maksimalno debelino sloja polimera.

Po izumu je konstrukcija CIM cevnega modula večjih volumnov rešena tako, da za konkreten sistem monomerne mešanice med polimerizacijo v trenutku, ko je dosežena maksimalna temperatura izračunamo toplotno prevodnost (λ_T) in specifično sproščeno toploto (S). S polimerizacijo enake mešanice pri različnih temperaturah določimo maksimalno dovoljeno temperaturno spremembo, ki ohranja željeno strukturo monolitnega poroznega polimera. Tako dobljene podatke uporabimo pri numeričnem reševanju enačbe 1 ali analitičnem reševanju enačbe 2 oziroma v primeru velikih zunanjih toplotnih uporov ustrezno modificiranih enačb. Na osnovi izbranega zunanjega polmera določimo debelino monolitne porozne polimerne cevi. Konstrukcija cevnega modula je prikazana na sliki 1 in poteka tako, da pripravimo več polimernih kosov v obliki cevi (1,2,3), natančno definirane debeline, tako da jih lahko vstavimo enega v drugega, torej, da je zunanji premer notranje cevi enak notranjemu premeru zunanje cevi (4) . Čeprav so prikazane le tri plasti, lahko modul skuonstruinrano iz poljubnega števila.

Tako pripravljen cevni modul vstavimo v ustrezno veliko ohišje podrobno opisano v patentni prijavi P-9800058. Ker s takim načinom priprave število plasti ni omejeno, lahko pripravimo CIM cevni modul poljubnega volumna.

za BIA d.o.o.

Aleš ŠTRANCAR

PATENTNI ZAHTEVEK

1. Konstrukcija CIM cevnega modula večjih volumnov

   označena s tem,

   da večplastno porozno polimerno cev vstavimo v ustrezno ohišje podrobno opisano v patentni prijavi P-9800058.

2. Večplastna porozna polimerna cev navedena pod točko 1

   označena s tem,

   da jo sestavimo iz poljubnega števila monolitnih poroznih polimernih cevi, natančno definirane debeline, tako da jih lahko vstavimo eno v drugo in se med seboj tesno prilegajo, da med njimi ni vmesnega prostora ter tvorijo večplastno porozno cev z notranjim premerom, ki je enak cevi z najmanjšim notranjim premerom in zunanjim premerom, ki je enak cevi z največjim zunanjim premerom

3. Večplastna porozna polimerna cev navedena pod točko 1

   označena s tem,

   da vsaka monolitna porozna polimerna cev vsebuje vsaj eno funkcionalno skupino, ki je lahko enaka pri vseh monolitnih poroznih ceveh, ali pa imajo različne monolitne porozne cevi različne funkcionalne skupine, ki so lahko razvrščene znotraj večplastne porozne polimerne cevi v poljubni kombinaciji.

4. Monolitna porozna polimerna cev navedena pod točko 2

   označena s tem,

   da je njena debelina manjša ali kvečjemu enaka debelini, ki jo izračunamo za konkreten sistem polivinilnega monomera, monovinilnega monomera, iniciatorja ter porgenov s tem, da določimo tekom polimerizacije toplotno prevodnost polimerne mešanice (λ_T), specifično sproščeno toploto (S), maksimalno dovoljeno temperaturno spremembo, ki ohranja zaželjeno strukturo polimera, na osnovi enačb 1 ali 2 oziroma ustrezno modificiranih enačb.

5. Monolitna porozna polimerna cev navedena pod točko 2

označena s tem,

da vsebuje polimer polivinilnega monomera, ki je izbran izmed divinilbenzena, divinilnaftalena, divinilpiridina, alkilen dimetakrilata, alkilen diakrilata, hidroksialkilen dimetakrilata, hidroksialkilen diakrilata, oligoetilen glikol dimetakrilata, oligoetilen glikol diakrilata, vinilestra polikarboksilne kisline, diviniletra, pentaerytritol di-, tri- ali tetrametakrilata ali akrilata, trimetiloilpropan trimetakrilata ali akrilata, alkilen bis akrilamida ali metakrilamida oziroma njihovih mešanic.

6. Monolitna porozna polimerna cev opisana pod točko 2

označena s tem,

da vsebuje polimer monovinilnega monomera, izbran iz skupine, ki vključuje stiren, stiren s substitucijo na obroču, vinilnaftalen, akrilate, metakrilate, vinilacetat, vinilpirolidon oziroma njihovo mešanico.

7. Monolitna porozna polimerna cev opisana pod točko 2

označena s tem,

da vsebuje majhne pore premera pod 200 nm kot tudi velike pore premera večjega od 600 nm in lahko dosežejo 2500 nm

8. Monolitna porozna polimerna cev opisana pod točko 2

označena s tem,

da je njena poroznost med 30 in 90%.

za BIA d.o.o.

Aleš ŠTRANCAR

IZVLEČEK

Konstrukcija CIM cevnih modulov večjih volumnov podaja način kako skonstruirati CIM cevni modul poljubnega volumna, pri katerem je struktura polimera homogena. Prav ta rešitev omogoča uporabo CIM cevnih modulov v industriji, kjer so zahtevani večji volumni.

Konstrukcija CIM cevnega modula večjih volumnov je rešena tako, da za konkreten sistem polimerne mešanice izračunamo toplotno prevodnost polimerne mešanice (λ_T) in specifično sproščeno toploto (S) na osnovi oblike temperaturnega profila polimerizacije enake polimerne mešanice v palici. S polimerizacijo enake mešanice pri različnih temperaturah določimo maksimalno dovoljeno temperaturno spremembo, ki ohranja nespremenjeno strukturo polimera. Tako dobljene podatke uporabimo pri numeričnem reševanju enačbe 1 ali analitični rešitvi enačbe 2 oziroma, v primeru večjih zunanjih toplotnih uporov, pri rešitvi ustrezno modificiranih enačb. Tako lahko na osnovi izbranega zunanjega polmera določimo maksimalno debelino polimerne cevi. Konstrukcija cevnega modula prikazana na sliki 1 poteka tako, da pripravimo več polimernih kosov v obliki cevi (1,2,3), natančno definirane debeline, z enakimi ali različnimi kemijsko aktivnimi skupinami, tako da jih lahko vstavimo enega v drugega, torej, da je zunanji premer notranje cevi enak notranjemu premeru zunanje cevi (4). Tako pripravljen CIM cevni modul vstavimo v odgovarjajoče ohišje podrobno opisano v patentni prijavi P-9800058.

Sl. 1

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(22)   *Application Date:*
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(54)   *Title:*
        Construction of Tubes With Larger Volumes

(21)   *Application No.:*
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For the Intellectual Property Office
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CONSTRUCTION OF CIM TUBES WITH LARGER VOLUMES

The object of the invention is the construction of CIM (Convective Interaction Media) tubes with larger volumes, applicable for preparatory separation and bioconversion.

The purification and isolation of molecules, especially of biopolymers, represents even to this day one of the most expensive stages in their attainment. Among biopolymers we include oligopeptides and polypeptides, proteins, enzymes, lectins, antibodies, nucleic acids, polysaccharides, oligonucleotides and polynucleotides.

Several methods of purification exist, such as, e.g. desalting with neutral salts, by changing the pH value, with electrophoresis, and with the use of chromatographic methods.

The first separation of proteins was, in all probability, carried out in 1954 (A.J.P. Martin and R.L.M. Synge, Biochem. J., 35 (1941) 1358) on DEAE cellulose. From those days we witnessed an intensive development of chromatographic carriers, as well as of different chemically active groups for separation. Towards the end of the fifties a company named Pharmacia (Uppsala, Sweden) introduced a cross-linked dextran gel for so-called size-exclusion chromatography for the separation of proteins and nucleic acids (German Patent 1,292,883; British Patent 974,054). Its use in chromatography was primarily limited by its low mechanical stability. In 1976 the first separation of peptides, on the basis of the so-called reverse phase chromatography, was published (K. Tsuji, J.H. Robinson, J. Chromatogr., 112 (1976)

663), followed by numerous articles about the separation of proteins with the aid of chromatography, based on size-exclusion, ion-exchange and reverse phase chromatography. The carriers that were employed were mechanically very stable, thus rendering high flows possible, and with them the shortening of the time necessary for separation. They possessed a structure of round particles, ranging in diameter from several 10 to 100μm, with a high degree of porosity, all of which resulted in a large specific surface, and connected with it, in a high capacity for the binding of biopolymers.

Biopolymers are large molecules (typically several 10 to several 100 kDa), consequently their diffusion coefficient is low (in the order of magnitude of 10^{-7} m^2/s). As the majority of the separation process is carried out in the pores of the particle carriers within which the liquid rests, the molecules travel to the active surface on the basis of diffusion, that limits the speeds of separation. Therefore, carriers of different structures were developed that were supposed to do away with problems in conjunction with diffusion. The first solution of this kind is represented by particles that are non-porous (for a review see, e.g.: W.-C. Lee, J. Chromatogr. B, 699 (1997) 29), where the entire separation process is carried out on the surface of the particle that is non-porous. This renders possible extremely quick analyses of biopolymers (several seconds), however, their main shortcoming is the low specific surface and, consequently, the low binding capacity. The second solution is represented by so-called perfusion particles (N.B. Afeyan, N.F. Gordon, I. Mazsaroff, L. Varady, S.P. Fulton, Y.B. Yang, F.E. Regnier, J. Chromatogr., 519 (1990) 1). Their characteristic being, that

beside closed pores they, likewise, possess flow pores. In contrast to non-porous particles they have a higher specific surface and binding capacity, as well as better hydrodynamic characteristics than porous particles. As they have particle structures, interstitial volume is still to be found between particles. Because it offers less resistance, the greatest portion of the liquid (over 90%) still flows around particles. The next step in the development of carriers is represented by monoliths. As distinguished from the afore mentioned carriers that are in the form of particles, monoliths are made up from a single piece of porous polymer material, containing flow pores (US Patent 4,889,632; US Patent 4,923,610). All of the liquid is forced to go through flow pores because there is no interstitial volume within the carrier. They distinguish themselves with their ability to quickly separate biopolymers (comparable to non-porous particles), a low back pressure even at higher flow rates, and a high capacity. Their usage in industrial applications was heretofore limited by problems in conjunction with the preparation of a homogeneous structure monolith of greater dimensions, as well as by poor mechanical stability. The solutions to these two problems are the objects of this Patent Application.

CIM tubes are made up from a housing, described in detail in Patent Application No. P - 9800058, that assures the mechanical stability and good distribution of the tubiform monolithic porous polymer. The monolithic porous polymer contains small pores with a diameter under 200 nm, as well as big pores with a diameter of up to 2500 nm. The porosity of the monolithic porous polymer is around 30 to 90%. The monolithic porous polymer includes a

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polyvinyl monomer polymer selected among divinylbenzene, divinylnaphthalene, divinylpyridine, alkylene dimethacrylate, alkylene diacrylate, hydroxyalkylene dimethacrylate, hydroxyalkylene diacrylate, oligoethylene glycol dimethacrylate, oligoethylene glycol diacrylate, vinyl ester of polycarboxylic acid, divinyl ether, pentaerythritol di-, tri- or tetramethacrylate or acrylate, trimethylopropane trimethacrylate or acrylate, alkylene bis acrylamide or methacrylamide, and mixtures thereof, respectively.

The monolithic porous polymer also includes the polyvinyl monomer as well as the monovinyl monomer copolymer. The latter was chosen from a group including styrene, ring substituted styrene, vinylnaphthalene, acrylate, methacrylate, vinylacetate, vinylpyrolidone, and mixtures thereof, respectively.

The initial monomer mixture further contains, beside monomers, a free-radical initiator, that together with monomers is dissolved in an inert organic solvent from the group of alcohols, esters of carboxylic acids or ketones, and mixtures thereof, respectively, with which different porosities of the final polymer are achieved.

The free-radical initiator is chosen from a group of azo compounds, peroxides, hydroperoxides, redox systems, or the like.

Reactive chemical groups can be entered on a monolithic porous polymer by means of a chemical modification, such as, e.g. with an alyl, amino, sulfonate, hydrogen sulfonate, hydroxyl, or alkyl length of up to 18 atoms. Likewise, different ligands can be

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immobilised on them, such as, e.g. peptides, oligonucleotide proteins, etc..

The working volume of a CIM tube described in Patent Application No. P - 9800058 is too small for it to be used in the majority of industrial processes. In the case of CIM tubes, volume can be increased in two ways: with the elongation of the tube, or with the enlargement of its diameter. Notwithstanding that the first possibility is more appropriate from the standpoint of separation quality, we should nevertheless be aware, that by elongation volume grows linearly, whereas by enlarging the diameter it grows exponentially, to the second power. The uniform distribution of the sample is a further problem that arises when elongating a CIM tube, as the route that the sample must travel, in order to cover the entire surface from beginning to end of the tube, is very long. From this it inevitably follows, that a further increase must be based, at least up to a certain point, on an increment of the diameter.

It is here that the problem of assuring the homogeneousness of the polymer arises. Polymerisation is, namely, an exothermic process. With suspension polymerisation, this phenomenon is not overly problematic, as mixing is present, and at the same time the beads within which polymerisation occurs are small in size. Polymerisation of larger tubes generates larger quantities of heat, that entails the creation of a temperature profile within the polymerisation solution. During polymerisation of a monolithic porous polymer, from which CIM tubes are made, it can come to a gel-effect, and consequently, the generation of heat in a short time span is so much the greater. As the pore size

distribution is highly dependent from temperature, the preparation of a polymer with a homogeneous structure defines the upper temperature within the polymer mixture, that must not be exceeded during polymerisation.

A resting period of the monomer mixture is, likewise, necessary for the restoration of a controlled structure. From this it follows, that the temperature profile within the polymer during polymerisation will depend on the quantity of specific generated heat, the heat conductivity of the polymer mixture, and the thickness of the polymer layer. As the first two factors represent characteristics of an individual polymer system we cannot influence them. Therefore, the thickness of the layer must be determined within which temperature changes remain low enough, so as not to affect the homogeneousness of the polymer structure. The maximum temperature within the monolithic porous polymer that has the form of a tube, and whose temperature had been set to the temperature of polymerisation on the internal and external sides, at a given inner and outer diameter, is calculated, based on the knowledge of heat conductivity of the polymer mixture and the specific heat generated, with the equation:

$$T_{max} = T_0 + \frac{S}{4\lambda_T} \cdot \left[r_z^2 + \frac{r_z^2 - r_n^2}{-\ln\left(\frac{r_n}{r_z}\right)} \cdot \left(\ln\left(\frac{1 - \left(\frac{r_n}{r_z}\right)^2}{-\ln\left(\frac{r_z}{r_n}\right)} \right) - 1 \right) \right] \qquad 1)$$

r_n -   inner diameter (m)

r_z -   outer diameter (m)

T_0 -   polymerisation temperature (K)

T_{max} -   maximum temperature reached within polymer (K)

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S   -   specific heat generated (W/m³)

λ_T -   heat conductivity of polymer mixture (W/mK)

In cases when the diameter is large enough, so as to make the error acceptable, an equation for a level plate can be used instead of equation 1, that goes as follows:

$$T_{max} = T_0 + \frac{S \cdot \left(\frac{r_z - r_n}{2}\right)^2}{2 \cdot \lambda_T} \cdot \left[1 - \frac{\left(\frac{r_n + r_z}{2}\right)^2}{\left(\frac{r_z - r_n}{2}\right)^2} \right] \qquad 2)$$

The two equations above include neither the external heat resistance of the model in which polymerisation is carried out nor the heat resistance of the buffer layer of the medium into which the mould with the mixture of monomers is inserted. When these resistances are significant the upper equations must be adequately modified.

From equations 1 and 2 respectively, the maximum thickness of the polymer layer, for the maximum regulation temperatures permitted, can be determined with a numerical solution.

According to the invention, the construction of a CIM tube with larger volumes is solved in a manner that the heat conductivity (λ_T) and the specific generated heat (S) are calculated for a concrete system of a monomer mixture during polymerisation, at the moment when the maximum temperature is reached. With the polymerisation of an equal mixture at different temperatures, the maximum permitted temperature change is determined, that preserves the desired structure of the monolithic porous polymer.

Thus obtained data are used for the numerical solution of equation 1 or for the analytic solution of equation 2, and in the case of large external heat resistances, for the solving of appropriately modified equations respectively. The thickness of a monolithic porous polymer tube is determined on the basis of a selected outer radius. The construction of a tube is shown on picture 1; it goes on by preparing several polymer tubiform pieces (1, 2, 3) that have a precisely defined thickness, so as to be able to insert them one into another, so that the outer diameter of the inner tube equals the inner diameter of the outer tube (4). The tube can be constructed from an optional number of layers, even though only three layers are shown.

A thus prepared tube is inserted into an adequately sized housing, thoroughly described in Patent Application No. P - 9800058. Because this mode of preparation does not limit the number of layers it is possible to prepare a CIM tube of any volume.

for BIA Ltd.
(signature)
Aleš ŠTRANCAR

1.   Construction of a CIM Tube With Larger Volumes

     marked by the fact,

     that the multilayered porous polymer tube is inserted
     into an adequate housing, thoroughly described in
     Patent Application No. P - 9800058.

2.   Multilayered Porous Polymer Tube, of Claim 1

     marked by the fact,

     that it is put together from an optional number of
     monolithic porous polymer tubes, having a precisely
     defined thickness, so as to be able to insert them one
     into the other in a way that they fit tightly between
     themselves, leaving no interstitial space, creating a
     multilayered porous tube with an inner diameter that
     is equal in size to the inner diameter of the smallest
     tube, and an outer diameter that is equal in size to
     the outer diameter of the largest tube.

3.   Multilayered Porous Polymer Tube, of Claim 1

     marked by the fact,

     that every monolithic porous polymer tube contains at
     least one functional group that can be equal for all

monolithic porous tubes, or else, different monolithic porous tubes have different functional groups that can be arranged within the multilayered porous polymer tube in an optional combination.

4. Monolithic Porous Polymer Tube, of Claim 2

marked by the fact,

that its thickness is smaller, or, at the utmost, equal to the thickness calculated for a concrete polyvinyl monomer, monovinyl monomer, initiator and porogene system, provided that during polymerisation the heat conductivity of the polymer mixture (λ_T), the specific generated heat (S), and the maximum permitted temperature change that preserves the desired polymer structure, are determined on the basis of equations 1 and 2, and adequately modified equations respectively.

5. Monolithic Porous Polymer Tube, of Claim 2

marked by the fact,

that it contains a polymer of a polyvinyl monomer, selected among divinylbenzene, divinylnaphthalene, divinylpyridine, alkylene dimethacrylate, alkylene diacrylate, hydroxyalkylene dimethacrylate, hydroxyalkylene diacrylate, oligoethylene glycol dimethacrylate, oligoethylene glycol diacrylate, vinyl ester of polycarboxylic acid, divinyl ether,

pentaerythritol di-, tri- or tetramethacrylate or acrylate, trimethylopropane trimethacrylate or acrylate, alkylene bis acrylamide or methacrylamide, and mixtures thereof respectively.

6. Monolithic Porous Polymer Tube, described in Claim 2

   marked by the fact,

   that it contains a polymer of a monovinyl monomer, selected from a group including styrene, ring substituted styrene, vinylnaphthalene, acrylate, methacrylate, vinylacetate, vinylpyrolidone, and mixtures thereof respectively.

7. Monolithic Porous Polymer Tube, described in Claim 2

   marked by the fact,

   that it contains small pores with a diameter under 200 nm, as well as big pores with a diameter greater than 600 nm , that can reach 2500 nm.

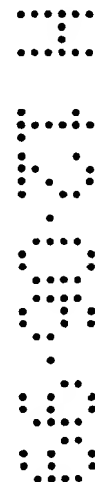8. Monolithic Porous Polymer Tube, described in Claim 2

   marked by the fact,

   that its porosity is between 30 and 90%.

for BIA Ltd.

(signature)

Aleš ŠTRANCAR

SUMMARY

The construction of CIM tubes with larger volumes offers a way of constructing a CIM tube that has a homogeneous polymer structure of any volume. It is precisely this solution that renders possible the use of CIM tubes in industry, where bigger volumes are necessary.

The construction of a CIM tube with larger volumes is solved in a manner, whereby the heat conductivity of the polymer mixture (λ_T) and the specific generated heat (S) are calculated for a concrete system of a polymer mixture, on the basis of the form of the polymerisation temperature profile of an equal polymer mixture in the rod. The maximum permitted temperature change that preserves the polymer structure unchanged is determined with the polymerisation of an equal mixture at different temperatures. Thus obtained data are used for the numerical solution of equation 1, or for the analytic solution of equation 2, and in the case of larger external heat resistances, for the solving of appropriately modified equations respectively. The maximum thickness of a polymer tube is determined on the basis of a selected outer radius. The construction of a tube is shown on picture 1; it goes on by preparing several polymer tubiform pieces (1, 2, 3) that have a precisely defined thickness, with equal or different chemically active groups, so as to be able to insert them one into another, so that the outer diameter of the inner tube equals the inner diameter of the outer tube (4). A thus prepared CIM tube is inserted into an adequate housing, thoroughly described in Patent Application No. P - 9800058.

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